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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,892	02/08/2002	Alison A. McCormick	42256	1133

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,892	MCCORMICK ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02.08.02; 03.08.04;* 01.11.05; 03.11.05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 51-57 are under examination

2. Claims 1-50 are cancelled in the preliminary amendment filed on February 8th, 2002.

Specification

3. The disclosure is objected to because of the following informalities:

The first line of specification needs to be updated with a priority statement claiming priority to U.S. provisional application 60/155,979 and U.S. Patent Application 09/522,900. For additional information on claiming benefit to an earlier filed application see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

Appropriate correction is required.

4. The use of the trademark in page 45 lines 5 and 6 (AGAROSE and SEPHADEX) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 52 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 recites the limitation "said product" in line 3. There is insufficient antecedent basis for this limitation in the claim. It is not clear as to what the applicant means by "said product" in claim 52. Does the phrase "said product" mean the scFv comprising the variable domains of the surface Ig of B cell lymphomas or any product produced by the method of claim 51?

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 51-57 rejected under 35 U.S.C. 103(a) as being unpatentable over Hawkins et al (WO 94/08008, International Publication Date 14 April, 1994; IDS: January 11, 2005) in view of Fiedler et al (Immunotechnology, 3(3):205-216, October 1997; IDS: March 08, 2004) and in view of Caspar et al. (Blood, 90(9):3699-3706, November 1997; IDS: January 11, 2005) and in view of Tang et al (J. Biol Chem. 271(26):15682-15686, June 1996; IDS: January 11, 2005) and further in view of Hakim et al (J. Immunol. 157:5503-5511, 1996; IDS: January 11, 2005).

9. The instant claims are drawn to a method of producing a single chain antibody comprising a first and second domain comprising the steps of: (a) joining a nucleic acid encoding the first domain of the polypeptide to a nucleic acid encoding a first part of a linker to produce a first nucleic acid construct; (b) joining the nucleic acid encoding a second part of the linker to a nucleic acid encoding the second domain of the polypeptide to produce a second nucleic acid construct; (c) incorporated said first and said second constructs into a transient plant expression vector in frame so that, when expressed, the polypeptide bears the first and second domain separated by the linker; (d) transfecting a plant with the vector so that the plant transiently produces the polypeptide; and (e) recovering the polypeptide' as a soluble, correctly-folded protein; wherein the polypeptide is a single chain wherein the first domain is the Ig VH domain and the second domain is Ig VL domain, both of which domains create an idiotype of a surface Ig of a B cell lymphoma, and wherein said product induces an idiotype-specific response directed to said lymphoma upon administration to a subject. The method is further limited wherein the plant is a plant cell. Further, the said domains are linked by an amino acid linker that has between one and 50 residues, that consists of between one and 12 different amino acids and facilitates secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell; wherein the linker is a member of a randomized library of linkers that vary in size and sequence, and said library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides such that position 1 of each repeated triplet cannot be the same nucleotide as position 2 of the repeated triplet,

position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet, or position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet; further, wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of deoxyadenosine (dA), deoxyguanosine (dG), deoxycytidine (dC), and deoxythymidine (dT); and further, wherein position 1 of each repeated triplet is dA or dG, position 2 of each repeated triplet is dC or dG, and position 3 of each repeated triplet is dT.

Hawkins et al teach the production of a single chain Fv (scFv) by joining a nucleic acid encoding the first domain of the polypeptide to a nucleic acid encoding a first part of a linker to produce a first nucleic acid construct with the nucleic acid encoding a second part of the linker to a nucleic acid encoding the second domain of the polypeptide to produce a second nucleic acid construct and incorporating the first and second constructs into a T vector so that, when expressed, the polypeptide bears the first and second domain separated by the linker (see figure 1, in particular).

Hawkins et al does not specifically teach the method of expression of above-mentioned polypeptide in a transient plant expression vector nor does it characterize the scFv, or does it specifically teach a randomized library of linkers with the instantly claimed criteria or does it teach that the first and second positions of each repeated triplet is selected from any two of dA, dG, dC, and dT or does it teach that above-mentioned polypeptide wherein position 1 of each repeated triplet is dA or dG, position 2 of each repeated triplet is dC or dG, and position 3 of each repeated triplet is dT.

These deficiencies are made up for in the teachings of Fiedler et al, Casper et al, Tang et al and Hakim et al.

Fiedler et al teach that scFv, which consists of variable light chain and variable heavy chain domain of an antibody molecule fused with a linker (see page 206 column 1, in particular), can be made in high quantities in transgenic plant cells, wherein 4-6% to 3-4% of the total protein found in soluble forms in leaves and seed, respectively, can be recombinantly expressed scFv. . Furthermore, Fiedler et al teach that such recombinant scFv is functionally active (see page 214 column 1, in particular).

Caspar et al teach an scFv obtained from a B-cell lymphoma Ig surface antigen. Because the scFv taught by Caspar et al is a scFv, it has two V-regions, one VH and one VL, wherein the VH region (see Figure 1, for example) includes at least one CDR, wherein it is a CDR2 (see page 3700, in particular) and is comprised of at least two domains. Furthermore, Caspar et al teaches that the scFv is linked together by a linker sequence. Moreover, Caspar et al teaches that although weak, the scFv administered did induce an immune response (see page 3702 column 2, in particular).

Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and that the length of the linker and sequence affect the expression level, solubility, stability and binding affinity of the scFvs (see page 15682 column 2, in particular). Tang et al teach a method of selecting active scFvs synthesized from libraries of scFv genes with randomized linker DNA sequences (see abstract and pages 15682-15684, in particular). Tang et al also teach the nucleotides within the linker to be

selected from dA, dG, dC or dT (see materials and methods: oligonucleotide synthesis, in particular).

Hakim et al teach immunotherapeutic compositions comprising a scFv constructed from the Ig variable regions from B cell lymphomas (i.e., idiotype) for inducing a polyclonal anti-idiotype response (see entire document). Hakim et al teach that the scFv needed to be conjugated to a strong carrier such as keyhole limpet hemocyanin (KLH) and mixed with an adjuvant to induce a tumor-protective anti-idiotypic response (see page 5503 column 1, in particular). Hakim et al also teaches that scFv-Il-2 and scFv-IFN-gamma as well as others enhanced the immunogenicity of the idiotype and elicited an anti-idiotype response that was protective against tumor challenge (see page 5503 column 2, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a single chain Fv as taught by Hawkins et al comprising B-cell Ig epitopes for therapeutic benefit of B cell lymphomas as taught by Caspar et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al such that the scFv induces an idiotype-specific response that would be protective against tumor challenge as taught by Hakim et al and to have produced the scFv in a plant as taught by Fiedler et al. One of ordinary skill in the art would have been motivated in doing so because Caspar et al teach the extraction and isolation of an antibody or Ig obtained from a B-cell lymphoma and the VH and VL domains of the surface Ig molecule are linked together with a linker and Tang et al teach a method of selecting active scFvs synthesized form libraries of scFv

genes with randomized linker DNA sequences. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized the construction of an scFv molecule as taught by Hawkins et al and optimize the scFv linker because Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and linker length and sequence affect the expression level, solubility, stability and binding affinity of the scFvs, and the one of ordinary skill in the art would have had a reasonable expectation of success because the scFvs with randomized linkers, wherein the nucleotides within the linker can be selected from dA, dG, dC or dT, were functionally active. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the scFv to elicit an idiotypic-specific response upon administration that would be protective against tumor challenge as taught by Hakim et al. In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a scFv comprising B-cell Ig epitopes for therapeutic benefit of B cell lymphomas as taught by Caspar et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al and further to have produced the scFv in a plant as taught by Fiedler et al because Fiedler et al teach that plant expression of scFvs offers a number of advantages including no requirement for complex culture media, sterility or large culture vessels, the possibility of composting plant waste material, no contamination with mammalian viruses or bacterial endotoxins, the latter two are especially important for producing scFvs intended for therapeutic use (see page 206 column 2, in particular). Furthermore, Fiedler et al teach that the plant material offers stable short- or long-term

storage of scFvs and is advantageous if the harvested material has to be transported or stored before further processing. Thus, it would have been prima facie obvious to one of ordinary skill in the at the time the invention was made to produce a scFv with a VH and VL joined by a linker as taught by Hawkins et al, comprising B-cell Ig epitopes for therapeutic benefit of B cell lymphomas as taught by Caspar et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al and to induce an idiotypic specific response that would be protective against tumor challenge as taught by Hakim et al and to have produced the scFv in a plant as taught by Fiedler et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the ad at the time the invention was made, as evidenced by the references.

Conclusions

10. No claims are allowed

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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(571) 272-8789

LARRY R. HELMS, PH.D
PRIMARY EXAMINER